L Number	Hits	Search Text	DB	Time stamp
1	4400	cytochrome adj P450	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/10/05 14:55
2	382771	encapsula$6 capsul$6 microencapsul$6	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/10/05 16:00
3	71	(cytochrome adj P450) SAME (encapsula$6 capsul$6 microencapsul$6)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/10/05 16:01
5	17	((cytochrome adj P450) AND (encapsula$6 capsul$6 microencapsul$6)).clm.	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/10/05 15:08
6	2161	(cytochrome adj P450) AND (encapsula$6 capsul$6 microencapsul$6)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/10/05 15:09
7	205	((cytochrome adj P450) AND (encapsula$6 capsul$6 microencapsul$6)) and porous	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/10/05 15:10
8	180	(((cytochrome adj P450) AND (encapsula$6 capsul$6 microencapsul$6)) and porous) and (cancer tumor neoplas$6)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/10/05 15:45
9	159	((((cytochrome adj P450) AND (encapsula$6 capsul$6 microencapsul$6)) and porous) and (cancer tumor neoplas$6)) and liver	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/10/05 15:46
10	88	(((((cytochrome adj P450) AND (encapsula$6 capsul$6 microencapsul$6)) and porous) and (cancer tumor neoplas$6)) and liver) and (prodrug cyclophos$9)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/10/05 15:46
16	47	((cytochrome adj P450) SAME (encapsula$6 capsul$6 microencapsul$6)) AND liver	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/10/05 16:01
17	11	GUNZBURG NEAR Walter	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/05 16:05
18	32	Salmons NEAR Brian	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/05 16:06
19	10	Saller NEAR Robert	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/05 16:07

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     (FILE 'HOME' ENTERED AT 14:38:59 ON 05 OCT 2004)

     FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED
     AT 14:40:49 ON 05 OCT 2004
L1         58948 S CYTOCHROME P450
L2        231698 S ENCAPUSLA? OR CAPSUL? OR MICROENCAPSUL? OR MICROSPHERE?
L3           115 S L1 (L) L2
L4            74 DUP REM L3 (41 DUPLICATES REMOVED)
L5            26 S L4 AND PY<=1997
L6            26 FOCUS L5 1-
L7            38 S L4 AND CELL?
L8            38 FOCUS L7 1-
                 E GUNZBURG WALTER??AU
                 E GUNZBURG WALTER?/AU
L9            54 S E2
L10            8 S E1
L11           62 S L9 OR L10
L12           51 DUP REM L11 (11 DUPLICATES REMOVED)
L13            7 S L12 AND L1
L14            7 SORT L13 PY

=> d an ti so au ab pi l14 1-7

L14  ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   1997:650467  CAPLUS
DN   127:315589
TI   Cytochrome P450 encoding retroviral vectors and their
     use as antitumor agents
SO   PCT Int. Appl., 25 pp.
     CODEN: PIXXD2
IN   Gunzburg, Walter H.; Karle, Peter; Saller, Robert Michael
AB   A replication-defective retroviral vector carrying a cytochrome P 450 gene
     under transcriptional control of target cell specific regulatory elements
     or promoters, or X-ray inducible promoters is disclosed.
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     ---------------     ----   --------    --------------------    --------
PI   WO 9735994          A2     19971002    WO 1997-EP1585          19970327
     WO 9735994          A3     19971120
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ,
             LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL,
             PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ,
             VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB,
             GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN,
             ML, MR, NE, SN, TD, TG
     CA 2250173          AA     19971002    CA 1997-2250173         19970327
     AU 9723827          A1     19971017    AU 1997-23827           19970327
     AU 713382           B2     19991202
     EP 892852           A2     19990127    EP 1997-919307          19970327
     EP 892852           B1     20040908
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
     NZ 331765           A      20000228    NZ 1997-331765          19970327
     JP 2000509249       T2     20000725    JP 1997-534051          19970327
     CZ 288074           B6     20010411    CZ 1998-3050            19970327
     RU 2185821          C2     20020727    RU 1998-119459          19970327
     SK 282744           B6     20021203    SK 1998-1323            19970327
     RU 2223788          C2     20040220    RU 2002-103465          19970327
     NO 9804540          A      19980928    NO 1998-4540            19980928
     US 6540995          B1     20030401    US 1999-442979          19991118

L14  ANSWER 2 OF 7  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   2000:207266  CAPLUS
DN   133:99184
TI   Intratumoral injection of encapsulated cells producing an oxazaphosphorine
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activating **cytochrome P450** for targeted chemotherapy
SO Advances in Experimental Medicine and Biology (1998), 451(Gene Therapy of Cancer), 97-106, 2 Plates
CODEN: AEMBAP; ISSN: 0065-2598
AU Karle, Peter; Muller, Petra; Renz, Renate; Jesnowski, Ralf; Saller, Robert; Von Rombs, Kerstin; Nizze, Horst; Liebe, Stefan; **Gunzburg, Walter H.**; Salmons, Brian; Lohr, Matthias
AB The prognosis of pancreatic adenocarcinoma is poor and current treatment is for the most part ineffective. We describe here a novel treatment strategy using a mouse model system for pancreatic cancer. Human embryonic epithelial cells have been genetically modified to express the cytochrome P 450 2B1 enzyme under the control of a CMV immediate-early promoter. This CYP2B1 gene converts oxazaphosphorines (ifosfamide or cyclophosphamide) to their active cytotoxic compds., phosphoramide mustard, which alkylates DNA, and acrolein, which alkylates proteins. A number of assays were performed to demonstrate the CYP2B1 gene function as well as toxic effects on neighboring cells (bystander effect). The cells were then encapsulated in a cellulose sulfate formulation shown to be well tolerated in the pancreas of immunocompetent mice, and injected 1 cm away from pre-established tumors derived from a human pancreatic tumor cell line (PaCa-44). I.p. administration of low-dose ifosfamide to tumor bearing mice that received the encapsulated cells results in partial or even complete tumor ablation. Such an in situ chemotherapy strategy utilizing genetically modified cells in an immuno-protected environment may prove useful for solid tumor therapy in man.

L14 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:412996 CAPLUS
DN 129:140515
TI Encapsulated cells engineered to produce an ifosfamide activating **cytochrome P450** in the vicinity of pancreatic tumors for targeted chemotherapy
SO Nucleic Acids Symposium Series (1998), 38(Advances in Gene Technology: Molecular Biology in the Conquest of Disease), 171-172
CODEN: NACSD8; ISSN: 0261-3166
AU **Gunzburg, Walter H.**; Karle, Peter; Muller, Petra; Jesnowski, Ralf; Nizze, Horst; Liebe, Stefan; Salmons, Brian; Lohr, Matthias
AB A system is developed for the local conversion of ifosfamide to the toxic forms at the site of pancreatic adenocarcinoma. Cells expressing cytochrome P 450 2B1 were encapsulated in cellulose sulfate and implanted in nude mice with human pancreatic adenocarcinoma, following the systemic treatment with ifosfamide. Of the 22 mice treated, 12 showed a reduction in tumor mass of >50%, and in 4 of these mice the tumor was no longer detectable. This therapeutic effect was due to the encapsulated cells since only .apprx.30% of the mice receiving ifosfamide alone (or non-encapsulated cells and ifosfamide) showed a benefit. In addition, the degree of necrosis was much higher in those mice receiving the encapsulated cells and ifosfamide.

L14 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:475624 CAPLUS
DN 132:44579
TI Injection of encapsulated cells producing an ifosfamide-activating **cytochrome P450** for targeted chemotherapy to pancreatic tumors
SO Annals of the New York Academy of Sciences (1999), 880(Cell and Molecular Biology of Pancreatic Carcinoma), 337-351
CODEN: ANYAA9; ISSN: 0077-8923
AU Muller, Petra; Jesnowski, Ralf; Karle, Peter; Renz, Regina; Saller, Robert; Stein, Hartmut; Puschel, Katrin; Von Rombs, Kerstin; Nizze, Horst; Liebe, Stefan; Wagner, Thomas; **Gunzburg, Walter H.**; Salmons, Brian; Lohr, Matthias
AB The prognosis of pancreatic cancer is poor, and current medical treatment is mostly ineffective. The aim of this study was to design a new treatment modality in an animal model system. We describe here a novel treatment strategy employing a mouse model system for pancreatic carcinoma. Embryonal kidney epithelial cells were genetically modified to express the cytochrome P 450 subenzyme 2B1 under the control of a cytomegalovirus (CMV) immediate early promoter. This CYP2B1 gene converts

ifosfamide to its active cytotoxic compds., phosphoramide mustard, which alkylates DNA, and acrolein, which alkylates proteins. The cells were then encapsulated in a cellulose sulfate formulation and implanted into preestablished tumors derived from a human pancreatic tumor cell line. I.p. administration of low-dose ifosfamide to tumor bearing mice that received the encapsulated cells results in partial or even complete tumor ablation. Such an in situ chemotherapy strategy utilizing genetically modified cells in an immunoprotected environment may prove useful for solid tumor therapy in man.

L14 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:475623 CAPLUS
DN 132:44445
TI Characterization of a human cell clone expressing **cytochrome P450** for safe use in human somatic cell therapy
SO Annals of the New York Academy of Sciences (1999), 880(Cell and Molecular Biology of Pancreatic Carcinoma), 326-336
CODEN: ANYAA9; ISSN: 0077-8923
AU **Gunzburg, Walter H.**; Karle, Peter; Renz, Renate; Salmons, Brian; Renner, Matthias
AB We have previously demonstrated the therapeutic effect and efficacy of implantation of cells genetically modified to express cytochrome P 450 2B1 in a nude mouse tumor model. The cells are encapsulated in polymerized cellulose sulfate and injected into preformed tumors. Upon administration of ifosfamide, the P 450 enzyme converts the ifosfamide into antitumorigenic toxic metabolites at the site required, thereby significantly reducing tumor burden. Feline kidney epithelial cells were chosen for these studies, because they are easy to culture and can readily be transfected. However, these cells are not suitable for eventual use in human patients, since they are known to express endogenous retroviruses that are able to infect mammalian cells. They thus represent a safety risk. Here we describe the establishment of a human cell line that has been genetically modified to express the same cytochrome P 450 construct and their characterization. The usefulness of mitomycin C treatment, both to protect the cells from the toxic metabolites that they produce and to incapacitate these cells from replicating, should they escape from the capsules, has also been investigated.

L14 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:297830 CAPLUS
DN 135:102137
TI Necrotic, rather than apoptotic, cell death caused by **cytochrome P450**-activated ifosfamide
SO Cancer Gene Therapy (2001), 8(3), 220-230
CODEN: CGTHEG; ISSN: 0929-1903
AU Karle, Peter; Renner, Matthias; Salmons, Brian; **Gunzburg, Walter H.**
AB Feline kidney cells were transfected with a vector overexpressing cytochrome P 450 2B1 (CYP2B1). Transfected cells acquired a new specific biochem. activity, which could be demonstrated by a rapid CYP2B1 detection assay and showed selective sensitivity to the antitumorigenic prodrug ifosfamide (IFO). Further, the cell-killing effect was also mediated on nonmodified cells like feline kidney cells, mouse lymphoma, and human pancreatic cells in the vicinity of the CYP2B1-expressing cells due to the diffusible nature of the activated IFO metabolites. One of these, phosphoramide mustard, causes interstrand DNA crosslinking and it has been thought that the inability to repair this damage results in apoptosis. Surprisingly, our results clearly demonstrate a necrotic mechanism of IFO-induced cell death. This may have important implications for the activation of the immune system during CYP2B1/IFO suicide gene therapy of cancer.

L14 ANSWER 7 OF 7 MEDLINE on STN
AN 2002466526 MEDLINE
TI A clinical protocol for treatment of canine mammary tumors using encapsulated, **cytochrome P450** synthesizing cells activating cyclophosphamide: a phase I/II study.
SO Journal of molecular medicine (Berlin, Germany), (2002 Sep) 80 (9) 610-4. Journal code: 9504370. ISSN: 0946-2716.

AU Winiarczyk Stanislaw; Gradski Zbigniew; Kosztolich Barbara; Gabler Cornelia; Konig Gerhardt; Renner Matthias; Saller Robert M; Prosl Heinrich; Salmons Brian; **Gunzburg Walter H**; Hain Johannes

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(FILE 'HOME' ENTERED AT 14:38:59 ON 05 OCT 2004)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 14:40:49 ON 05 OCT 2004

L1 58948 S CYTOCHROME P450
L2 231698 S ENCAPUSLA? OR CAPSUL? OR MICROENCAPSUL? OR MICROSPHERE?
L3 115 S L1 (L) L2
L4 74 DUP REM L3 (41 DUPLICATES REMOVED)
L5 26 S L4 AND PY<=1997
L6 26 FOCUS L5 1-
L7 38 S L4 AND CELL?
L8 38 FOCUS L7 1-

=> d an ti so au ab pi l8 1 4 5

L8 ANSWER 1 OF 38 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:546443 CAPLUS
DN 138:78227
TI Microencapsulation of genetically engineered **cells** for cancer therapy
SO Methods in Enzymology (2002), 346(Gene Therapy Methods), 603-618 CODEN: MENZAU; ISSN: 0076-6879
AU Loehr, J.-Matthias; Saller, Robert; Salmons, Brian; Guenzburg, Walter H.
AB The use of genetically engineered, microencapsulated **cells** in cancer therapy using pancreatic carcinoma as a model system is described. Thus, transgenic **cells** expressing the rat CYP2B1 gene are encapsulated using sodium **cellulose** sulfate and poly(diallyldimethylammonium chloride). The encoding cytochrome P 450 converts ifosfamide into phohsphoramide and acrolein. (c) 2002 Academic Press.

L8 ANSWER 4 OF 38 MEDLINE on STN
AN 1999344366 MEDLINE
TI Characterization of a human **cell** clone expressing cytochrome P450 for safe use in human somatic **cell** therapy.
SO Annals of the New York Academy of Sciences, (1999 Jun 30) 880 326-36. Journal code: 7506858. ISSN: 0077-8923.
AU Gunzburg W H; Karle P; Renz R; Salmons B; Renner M
AB We have previously demonstrated the therapeutic effect and efficacy of implantation of **cells** genetically modified to express **cytochrome P450** 2B1 in a nude mouse tumor model. The **cells** are encapsulated in polymerized **cellulose** sulphate and injected into preformed tumors. Upon administration of ifosfamide, the P450 enzyme converts the ifosfamide into antitumorigenic toxic metabolites at the site required, thereby significantly reducing tumor burden. Feline kidney epithelial **cells** were chosen for these studies, because they are easy to culture and can readily be transfected. However, these **cells** are not suitable for eventual use in human patients, since they are known to express endogenous retroviruses that are able to infect mammalian **cells**. They thus represent a safety risk. Here we describe the establishment of a human **cell** line that has been genetically modified to express the same **cytochrome P450** construct and their characterization. The usefulness of mitomycin C treatment, both to protect the **cells** from the toxic metabolites that they produce and to incapacitate these **cells** from replicating, should they escape from the **capsules**, has also been investigated.

L8 ANSWER 5 OF 38 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:550780 CAPLUS
DN 138:100500
TI Microencapsulated, CYP2B1-transfected **cells** activating ifosfamide at the site of the tumor: The magic bullets of the 21st century
SO Cancer Chemotherapy and Pharmacology (2002), 49(Suppl. 1), S21-S24 CODEN: CCPHDZ; ISSN: 0344-5704
AU Lohr, Matthias; Hummel, Frank; Faulmann, Grit; Ringel, Jorg; Saller, Robert; Hain, Johannes; Gunzburg, Walter H.; Salmons, Brian

AB Conventional chemotherapy of pancreatic carcinoma is only marginally effective. This is in part due to the severity of side effects following systemic administration of the cytostatic drug. The aim was to create a therapeutic tool allowing the targeting of the conversion site of a cytotoxic prodrug to the site of the tumor. This was realized by transfection of the CYP2B1 gene, the major ifosfamide-converting P 450 enzyme, in **cells** with subsequent microencapsulation and administration of these microcapsules to or into the tumor. The enzyme activity (resorufin assay) remained stable for weeks in vitro and in vivo within the microencapsulated CYP2B1-expressing **cells**. We demonstrated a significant antitumor effect of the intratumorally injected capsules against xenotransplanted human pancreatic carcinomas in the nude mouse. Angiog. expts. in the pig confirmed the feasibility of an intraarterial placement of the capsules into the pancreas. A clin. protocol was established and approved. L293 **cells** were transfected with the CYP2B1 gene, microencapsulated (diameter 0.7 mm) under GCP conditions and packed sterile. Patients with confirmed inoperable adenocarcinoma of the pancreas underwent angiog., and capsules were injected into a vessel leading into the tumor. The patients were monitored for 48 h to exclude allergic reactions or pancreatitis. A day later, ifosfamide was administered for three consecutive days to be repeated on days 21-23. The patients were followed up for 5 mo. A total of 17 patients were enrolled. The patients tolerated the procedure without any complications. No allergic reactions or pancreatitis were encountered. Chemotherapy was uneventful. All patients had stable disease, and two patients a partial remission. The median survival was 44 wk which compared favorably with that of a historical control group (22 wk). The intraarterial administration of microcapsules for targeted chemotherapy was well tolerated. Control of local tumor growth was achieved.

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